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Pso: psoriasis; PsA: psoriatic arthritis
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Abbreviations used: HS = hidradenitis suppurativa; IL = interleukin; LTB4 = leukotriene B4, PAF = platelet-activating factor; HiSCR= Hidradenitis Suppurativa Clinical Response; MASP = mannose associated serine protease; KK= kallikreins; MMP = Matrix metalloproteinase; Treg = CD4+ FoxP3+ $CD127_{low}$ regulatory cells; PASH= pyoderma gangrenosum, acne, suppurative hidradenitis; MAC = membrane attack complex; PAD4 = petidylarginine deiminase 4; HOCl = hypochlorous acid; ROS = reactive oxygen species; 5-LOX = 5-lipoxygenase (5-LOX); MAPK = mitogen-activated protein kinase; IBD = inflammatory bowel disease; Cat G = Cathepsin G; PAMPS = pathogen-associated molecular patterns; PRRs = pattern recognition receptors; RCTs = randomized-controlled trials; LCN-2 = Lipocalin-2; HC =healthy controls; HMWK = high molecular weight kininogen;

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What is already known about this topic?

- Recruitment of neutrophils to HS lesions may play an essential role in the development of the inflammatory nodules and abscesses that characterize the disease.

What does this study add?

- This study reviews inflammatory molecules known to be elevated in HS, and discusses their roles in recruiting, activating, and assisting neutrophils.

- It also highlights pharmacologic interventions that could be used or developed to target the specific immune pathways involved with neutrophils for HS treatment.

Abstract

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent, and debilitating skin disease of the hair follicle unit that typically develops after puberty. The disorder is characterized by comedones, painful inflammatory nodules, abscesses, dermal tunnels, and scarring, with a predilection for intertriginous areas of the body (axillae, inguinal, and anogenital regions). Recruitment of neutrophils to HS lesion sites may play an essential role in the development of the painful inflammatory nodules and abscesses that characterize the disease. This is a review of the major mediators involved in the recruitment of neutrophils to sites of active inflammation including bacterial components (endotoxins, exotoxins, capsule fragments, etc.), the complement pathway anaphylatoxins C3a and C5a, tumor necrosis factor-alpha (TNF- α), interleukin 17 (IL-17), interleukin 8 (CXCL8/IL-8), interleukin 36 (IL-36), interleukin 1 (IL-1), lipocalin-2, leukotriene B4 (LTB4), platelet-activating factor, kallikrein, matrix metalloproteinases (MMPs), and myeloperoxidase inhibitors. Pharmacologic manipulation of the various pathways involved in the process of neutrophil recruitment and activation could allow for successful control and stabilization of HS lesions and the remission of active, severe flares.

Introduction

Neutrophils are part of the front-line defense of host immune responses against invading pathogens. The rapid migration of neutrophils from the circulation to a site of inflammation is controlled by interactions with the vascular endothelium. L-selectin expressed on the surface of neutrophils allows loose tethering to ligands expressed on the surface of endothelial cells as it rolls along the endothelium. Rolling arrest is mediated by binding of chemoattractants such as CXCL8/IL-

8 to neutrophil receptors following high-affinity adherence to the endothelium. Neutrophils then migrate into the tissue through paracellular and transcellular migration, with a small minority penetrating and passing through pores in the cytoplasm of endothelial cells. Once at the tissue site of inflammation, the neutrophils engage and kill microorganisms and clear infections via different mechanisms such as chemotaxis, phagocytosis, liberation of cytokines, and neutrophil extracellular traps (NETs). Further, a large body of evidence has indicated the importance of neutrophils not only in innate immunity but also in the modulation of adaptive immune responses.[1,2]

One disorder in which neutrophil recruitment may play an important role is hidradenitis suppurativa (HS). HS is a recurrent debilitating skin disease of the hair follicle unit that predominantly affects females compared to males, in the United States and Europe.[3] HS is characterized by painful inflammatory nodules, abscesses, comedones, dermal tunnels, and scarring in folded skin rich in apocrine glands, the axillae, inguinal, and anogenital regions. [4] Suppuration is one of the clinical hallmarks of HS, presenting both acutely in abscesses and as chronic drainage of dermal tunnels.

Numerous studies suggest contribution of both genetic susceptibility (e.g. γ- secretase mutations) and dysregulation of the innate and adaptive immune pathways in HS pathogenesis. [5-8] A recently proposed mechanism for development of HS lesions suggests that, in predisposed individuals, dilated hair follicles in intertriginous areas may first rupture into the dermis. Next, the hair follicle contents, including commensal microbiota and keratin, appear to initiate an innate immune response. Activated inflammasomes may release IL-1 further driving the production of pro-inflammatory cytokines including TNF, IL-6, and interferon-gamma (IFN- γ). These pro-inflammatory cytokines, in turn, lead to dendritic cell activation which produces IL-23. IL-23, in turn, has been shown to promote the expansion/maintenance of CD4+ T helper 17 (Th17) cells.[9,10] Moreover, the ratio of Th17 cells to CD4+ FoxP3+$CD127_{low}$ regulatory (Treg) cells is highly dysregulated in HS lesional skin owing to the increase in IL-17 producing Th17 cells, and this Th17/Treg axis imbalance may negatively affect Treg-controlled hair follicle stem cell homeostasis and infundibular integrity.[11,12] The keratinocyte response also results in the increased production of TNF and antimicrobial peptides[17,18].

Among the numerous functions of neutrophils, of particular interest is the formation of NETs. These web-like structures are released from the neutrophils into the extracellular space after exposure to various danger signals to trap and kill microbes.[13] During NET formation, petidylarginine deiminase 4 (PAD4) is activated, promoting histone citrullination. Byrd et al showed that enhanced NET formation in HS externalizes autoantigens that are recognized by HS serum antibodies. Specifically, some of the antibodies recognizing citrullinated peptides such as those on histones were detected in the serum of HS patients.[14]

Thus, migration of neutrophils to lesion sites may play an essential role in the development of characteristic HS lesions (Figure 1). Pharmacologic manipulation of the various pathways involved in this process could allow for successful reduction of neutrophilic migration and activation, leading to reduction in suppurative discharge, control of HS symptomatology, and improvement in disease activity. The following review outlines the immunologic pathways that lead to neutrophil activation, recruitment, and migration, discusses the data for neutrophil involvement in the pathogenesis of HS, and reveals potential pharmacologic interventions that could be used or developed to target specific immune pathways for the treatment of HS (Table 1).

Bacterial Components

The innate immune system relies on recognition of evolutionarily conserved structures on pathogens termed pathogen-associated molecular patterns (PAMPs) and on a limited number of germ-line encoded pattern recognition receptors (PRRs) (e.g. Toll-Like receptors (TLRs)). Upon PAMP recognition, PRRs present at the cell surface or intracellularly, signal to the host the presence of infection and trigger a multitude of proinflammatory and antimicrobial responses that ultimately lead to the expression and synthesis of a broad range of molecules including cytokines, chemokines, cell adhesion molecules, and immunoreceptors.[15] Bacteria can attract neutrophils directly through stimulation by antigens or by damaging cells.[16,17] Thus, antibacterial therapies can be a method to decrease antigen-mediated neutrophil chemotaxis and inflammation in HS lesions.

Previous microbiological studies found a wide range of bacteria sporadically associated with HS lesions: *Prevotella*, *Porphyromonas*, *Fusobacteria, Parvimonas, Staphylococcus* lugduinensis, milleri group streptococci, actinomycetes species, and *Staphylococcus* aureus.[18-21]

Antibiotics have long been a part of HS treatment, including topical clindamycin, oral tetracyclines, combination oral rifampicin and clindamycin, as well as triple antibiotics with metronidazole, rifampicin, and a quinolone.[22-25] Further, clindamycin has been found to inhibit complement-derived chemotaxis of polymorphonuclear leukocytes *in vitro* and may enhance the uptake of microorganisms by the phagocytic cells of the host. Rifampin may work in HS though its capacity to alter the secretion of cytokines by human monocytes, and tetracyclines have also been shown to inhibit CXCL8/IL-8 and neutrophil activation.[26-30] Recently, intravenous ertapenem has also been shown to be effective in patients with severe disease that did not respond to other treatments, especially as a bridge to biologics or surgery [46-48] However, further research involving large-scaled randomized controlled trials (RCTs) is needed to fully elucidate the effects of antibiotics in HS patients, and to develop effective combinations for maintenance therapies.

Anaphylatoxins and complement system

Complement is an ancient system that responds to stimuli such as bacteria to recruit neutrophils and activate the innate immune system, [31,49] and its components have been shown to be elevated in HS serum and tissue. [32-34] In the presence of immune dysregulation, dysbiosis and bacterial overgrowth may activate the complement pathway leading to the excess production of complement 5a (C5a) and inflammatory cytokines resulting in the recruitment of neutrophils and inflammatory cells to the affected area causing abscess formation and suppurative discharge. [33] Briefly, activation of the classical, lectin, or alternative pathways produces C3 convertase, which subsequently induces a C5 convertase and the membrane attack complex (MAC) which can damage and opsonize pathogen cells. Byproducts C3a and C5a are potent anaphylatoxins, recruiting neutrophils and activating the inflammasome. [31]With the increased levels of neutrophils in HS lesions and increased circulating complement levels in HS patients, complement mediating therapies offer potential treatment options for patients.

There are both indirect and direct agents that target the complement pathway. Corticosteroids are well known immune modulators, impacting the polyclonal hypergammaglobulinemia in HS. [35-37] A direct anti-C5a antibody IFX-1 is currently in phase II trials for the treatment of HS. While promising safety and efficacy results were reported for the initial small open label study,[38] there was no significant difference compared to placebo in a larger RCT. [39] An open-label extension study is

ongoing. [40] Avacopan, a C5a receptor 1 inhibitor, is currently in phase II clinical trials for the treatment of moderate to severe HS (NCT03852472). Other anti-complement treatments in development that have not yet been explored in HS, include C1 esterase inhibitors, anti-C5 antibodies (Eculizumab, Ravulizumab), C3 inhibitor peptides, a protein inhibitor of C3 convertase, and anti-factor B, anti-factor D and anti-properdin therapies.

TNF-alpha

Resting neutrophils can become primed by agents that include bacterial products and cytokines or chemokines (e.g. TNF-α, GM-CSF, CXCL8/IL-8 and IFN-γ).[41] TNF-α primes the neutrophil respiratory burst, up-regulates the expression of adhesion molecules, cytokines, and chemokines, and at high local concentrates can stimulate reactive oxygen species (ROS) production in adherent neutrophils to trigger bacterial killing.[2]

Adalimumab, a monoclonal antibody against TNF, is the only currently Food and Drug Administration approved systemic medication for treatment of HS. Other TNF inhibitors include infliximab, etanercept, golimumab, and certolizumab. In a phase II study of 38 patients with moderate-to-severe HS, more patients treated with infliximab experienced a 50% or greater decrease in the Hidradenitis Suppurativa Severity Index (HSSI) in comparison to those on placebo.[42] No significant improvement in HS was found in patients given etanercept 50mg twice weekly for 24 weeks.[43] Golimumab has only been used in two case reports: in the first one, it did not result in clinical improvement of HS,[44] while in the second case presenting with HS and pyostomatitis vegetans on a background of ulcerative colitis, it resulted in complete and sustained remission of the overall clinical picture.[45] Finally, certolizumab was used in two HS patients but found to be ineffective.[46] However, a recent case report showed complete resolution of nodules and abscesses after 3 months of treatment.[47]

IL-17

IL-17, in cooperation or synergism with other inflammatory mediators, can induce a potent inflammatory cascade by upregulating a wide array of target genes that includes induction of neutrophil-specific chemokines (CXCL1, CXCL2, CXCL5, CXCL8). In addition to Th17 cells, innate

lymphoid cells, γ-δ T cells, mast cells, and neutrophils have been shown to produce IL-17. [48,49] Dermal IL-17 and T helper 17-enhanced responses drive neutrophil migration into affected areas and promote tissue damage. [50,51] Therefore, blocking IL-17 or the downstream effects of IL-17 may serve as a potential therapy in HS. [52]

IL-17 has been shown to be elevated in the serum of classic HS patients, [53,54] and tissues of classic and syndromic HS, [50,51,54,55] and IL-17 producing neutrophils are prominent in affected HS lesional skin. [50] Case reports have suggested that targeting IL-17 is a promising therapeutic approach for HS. [56-58] Phase III clinical trials are currently underway testing the safety and efficacy of using secukinumab, a fully human antibody that targets IL-17A, in the treatment of HS (NCT03713632). However, IL-17 blockade can also be the trigger of paradoxical HS. [57] The activation of type 1-IFN as well as IL-1β and/or other proinflammatory cytokines/chemokines may explain the occurrence of paradoxical HS. [59] Previous studies have demonstrated that HS is associated with a significantly increased risk of co-occurring and new-onset IBD[60]; secukinumab has been associated with worsening symptoms compared to placebo in clinical trials of Crohn's disease and therefore, the onset and/or worsening of IBD needs to be closely monitored for in phase 3 trials.[61,62] Another IL-17 inhibitor that is under phase III studies for psoriasis that could potentially be used for HS includes ixekizumab. [63,64] A recent open-label cohort study of 10 patients treated with subcutaneous brodalumab (anti-17A, IL-17C and IL-17F) showed promising results.[65] Bimekizumab (dual IL-17A and IL-17F inhibitor) is currently under phase II multicenter clinical trials for moderate-to-severe HS (NCT03248531).

IL-8/CXCL8

IL-8/CXCL8 primarily functions to induce chemotaxis of neutrophils to the site where they are needed.[66,67] Alterations of CXCL8/IL-8 resulting in increased levels in both the skin and serum have been reported in patients with both classic HS and PASH (pyoderma gangrenosum, acne, suppurative hidradenitis). [55,68,69] In addition, CXCL 1/2/3 has been shown to be elevated in PG, PASH, and PAPASH (pyoderma gangrenosum, acne, suppurative hidradenitis, pyogenic arthritis).[70] Currently, anti-IL8 treatments, such as Repertaxin[71,72] and Sivelestat [73], have not yet been explored in HS.

IL-36

IL-36α, IL-36β and IL-36γ are recently reported pro-inflammatory agonists in the IL-1 superfamily. They play an important role in the regulation of both the innate and adaptive immune systems and induce proinflammatory signaling pathways via the activation of nuclear factor-κB and mitogen-activated protein kinase.[98-101] IL-36 (α, β, γ) is presumed to act as a bridge in the activation of innate and adaptive immune responses, fostering IL-1β, IL-6, TNF-α, and IL-23p19. These cytokines have been shown to be involved in the generation of a Th17 immune response.[74] In addition, NETs have neutrophil granule proteases, Cathepsin G (Cat G), elastase, and proteinase-3 (PR-3). NET-associated proteases, particularly Cat G, robustly process and activate IL-36α, IL-36β, and IL-36γ as well as IL-1α, thereby activating the biological activity of these cytokines.[75]

A recent study has shown that the expression levels of IL-36α, IL-36β, IL-36γ, and IL-36R were all significantly higher in lesional HS skin than in healthy controls.[76] No IL-36 inhibitors are currently under testing for HS; however, a phase 1 proof-of-concept study involving patients with generalized pustular psoriasis treated with BI 655130, a monoclonal antibody against the IL-36 receptor (NCT02978690), showed good results.[77]

IL-1

IL-1 has been shown to increase neutrophil migration through upregulation of IL-8/CXCL8. [78] When HS cytokine patterns were further examined, IL-1β turned out to be a highly prominent cytokine, overexpressed even compared with psoriatic lesions.[79] IL-1 signaling is also important for adaptive immune responses.[80]

In a RCT of 20 patients with HS, HS disease activity score was significantly decreased in the arm treated with anakinra (IL-1 type 1 receptor antagonist) (7 of 9) vs the placebo group (2 of 10) after 12 weeks, (but not at 24 weeks) ($P = 0.02$).[81] In later case reports, there were also experiences of severe HS proving refractory to anakinra.[82] In a phase II, multi-center, open label study of HS patients treated with subcutaneous bermekimab (IL-1α inhibitor), approximately 60% of patients achieved HiSCR.[83] Canakinumab, an anti- IL-1β antibody, has been given subcutaneously up to 150 mg per week for the treatment of HS with conflicting results in case reports and series.[84-88]

Lipocalin-2

Lipocalin-2 (LCN-2) is a secreted mediator found in the neutrophil secondary granules, and is expressed de novo by macrophages and epithelium in response to inflammation.[89] *In vitro,* LCN-2 stimulated human neutrophils to produce vital proinflammatory mediators, such as IL-6, CXCL8/IL-8, TNF-α, and IL-1α via a specific receptor, 24p3R, on neutrophils.[90] Blood samples of patients with HS have demonstrated significantly elevated levels of LCN-2 in comparison to healthy controls.[91] Strongly elevated LCN-2 expression was also present in HS lesions, with granulocytes and keratinocytes being sources of this expression. Further, TNF-alpha was found to be a significant inducer of LCN-2 from keratinocytes. A highly significant positive relationship between LCN-2 levels and HS disease severity was demonstrated using the Sartorius score. LCN-2 levels were also found to be positively associated with the number of affected body areas in HS.[91] Currently, no medications directly targeting LCN-2 exist on the market or in clinical trials.

LTB4

LTB4 is an inflammatory molecule (leukotriene) produced by leukocytes from arachidonic acid, specifically via the 5-lipoxygenase pathway.[92] Of all the leukotrienes, LTB4 is the most potent chemoattractant for neutrophils, and is able to induce the formation of ROS and the release of lysosomal enzymes by neutrophils.[93]

A recent lipidomics study found increased LTB4 in HS lesions.[94] In an open-label clinical trial using ustekinumab for HS, clinical responders were found to have lower expression levels of leukotriene A4-hydrolase (LTA4H) suggesting that leukotriene may play an important role in the inflammation of HS. [95] A potential LTA4H inhibitor for HS is ubenimex, and 5-lipoxygenase (5-LOX) inhibitors may also be useful, [96,97] including zileuton,[125] atreleuton and setileuton. [98]

PAF

Platelet-activating factor is well known to stimulate neutrophil migration toward the stimulus of injury in acute inflammation.[99] PAF activates neutrophils by stimulating their mitogen-activated protein kinase (MAPK) and p38 signaling pathways.[100] Additionally, PAF mediates neutrophil adhesion onto activated platelets, a process that is critical during the rolling phase of neutrophil migration toward tissue.[101] Evidence for the specific role of PAF in HS has not been published to

date. Synthetic rupatadine, an oral PAF and histamine H1 receptor antagonist, has not yet been trialed in HS.

Phytochemical products such as ginkgolides are either competitive antagonists or partial agonists of the PAF system. [102] At the pharmacodynamic level, *ginkgo biloba* is known to inhibit key neutrophil mediators including ROS production, selectin-mediated adhesion, and NF-KB-dependent inflammation. [103] Within the dietary realm, olive oil, grapes, honey, fish, and dairy consist of numerous products that exert anti-PAF activities. Mediterranean diets, as well as those incorporating garlic, soy sauce, turmeric, and tea, may benefit from small-molecule PAF-inhibition, though the evidence is limited. [102,104] However, despite promising data, PAF antagonists have previously failed to exhibit benefit in clinical trials relating to PAF-mediated inflammation in sepsis, acute pancreatitis, and asthma.[105]

Kallikrein

Kallikreins (KKs) are part of the plasma contact activation system, a component of the innate immune system, that is spontaneously activated by negatively charged surfaces (e.g. bacterial or fungal surfaces). Once activated, kallikrein has been shown to cleave the central complement component C3 directly to yield active components C3b and C3a. Kallikrein can also cleave high molecular weight kininogen (HMWK) to release the proinflammatory peptide bradykinin, which in turn causes vascular leakage and the sensation of pain.[106] Direct expression of KKs in HS has not yet been studied. However, KKs provide critical regulatory roles to skin cathelicidins such as LL-37,[107] which has been shown to be increased in HS lesions and lead to increased immunoreactivity and neutrophil recruitment to the local perifollicular epidermis. [108,109] Ecallantide, an inhibitor of plasma kallikrein, has been shown to reduce neutrophil-mediated kallikrein activity and elastase release in *in-vitro* studies.[110]

Matrix Metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs), zinc-dependent proteolytic enzymes, have been shown to play a role in the recruitment of neutrophils to sites of inflammation. MMPs facilitate extravascular migration of neutrophils through the extracellular matrix by degrading the matrix. [111] Further, MMP-9

exists in neutrophils and is released upon neutrophil activation further potentiating the cycle. [112] High lesional and serum MMP-8 levels have been found in HS patients. [113] Increased expression of matrix-degrading enzymes (MMP 1,3,9 and 10) in HS skin lesions was paralleled by down-regulation of tissue inhibitor of matrix metalloproteinases (TIMP, an important inhibitor of MMP activity). This resulted in strongly increased MMP/TIMP4 ratios in HS, indicating an extraordinary activity of these enzymes in HS linked to the destructive character of the disease. [79] Tetracyclines (e.g. doxycycline, minocycline) are antibiotics that can chelate the Zn^{2+} ion and thereby inhibit MMP activity. [114] Currently, tetracyclines are recommended for use in mild-to-moderate HS for a 12-week course or as long-term maintenance therapy when appropriate.[115]

Myeloperoxidase Inhibitor

Dapsone exerts its anti-neutrophilic effect by inhibiting the myeloperoxidase-H_2O_2-halide-mediated cytotoxic system. As part of the respiratory burst that neutrophils use to kill bacteria, myeloperoxidase converts hydrogen peroxide into hypochlorous acid (HOCl). HOCl is the most potent oxidant generated by neutrophils and can cause significant tissue damage during inflammation. Dapsone arrests myeloperoxidase in an inactive intermediate form, reversibly inhibiting the enzyme, thus interfering with neutrophil function. However, in a case series of 24 HS patients receiving dapsone, improvement was only seen in 9 out of 24 (38%) treated patients. None of the 4 cases with severe disease experienced improvement. Recurrence of disease at the cessation of treatment was described as rapid. [116]

Conclusion

Numerous physiologic pathways exist to recruit, activate, and assist neutrophils in the context of inflammation. A thorough understanding of the various cytokines and other molecules involved in these processes could be invaluable in the development of new targeted therapies or the re-purposing of existing therapies for the treatment of HS by inhibiting neutrophil recruitment and activation.

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Figure 1. Neutrophil migration towards active HS lesions. At the site of an active HS lesion, commensal microbiota initiate an immune response and the complex biological process of inflammation occurs, along with all its associated mediators (e.g. cytokines, chemokines, leukocytes, etc.). Circulating neutrophils respond to these mediators and extravasate from the vasculature via diapedesis, intent on reaching the site of inflammation from which these mediators are originating. Neutrophils eventually reach the site of inflammation via chemotaxis along an ever-increasing chemoattractant gradient—one that is further augmented by a positive feedback loop of arriving-neutrophilic contents—potentiating the initial inflammatory response.

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Table 1. NEUTROPHIL FUNCTION IN HIDRADENITIS SUPPURATIVA (HS)		
Therapeutic Targets	**Inhibitors**	**Comments on Inhibitors**
Bacterial Components (endotoxins, exotoxins, capsule fragments, etc.)	Antibiotics[22-25,46-48]	Those most commonly indicated in HS include topical clindamycin, oral tetracyclines, combination oral rifampicin/clindamycin, triple antibiotics with metronidazole, rifampicin, and a quinolone, and IV ertapenem
Anaphylatoxins (C3a and C5a)	IFX-1[39,40]	A direct anti-C5a antibody that is currently in phase II trials for the treatment of HS
	Avacopan (NCT03852472)	A C5a receptor 1 inhibitor that is also currently in phase II trials for the treatment of moderate to severe HS
	Eculizumab, Ravulizumab	Anti-C5 antibodies that are currently indicated for the treatment of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and neuromyelitis optica
	Theoretical treatments yet to be explored	C1 esterase inhibitors, C3 inhibitors, C3 convertase inhibitors, anti-factor B, anti-factor D, anti-properdin
Tumor Necrosis Factor-Alpha (TNF- α)	Adalimumab, Infliximab, Etanercept, Golimumab, & Certolizumab[42,44-47]	Adalimumab is the only Food and Drug Administration approved systemic medication for HS

Myeloperoxidase Inhibitor	Dapsone[116]	Inhibits myeloperoxidase-H_2O_2-halide-mediated cytotoxic system in an inactive intermediate form, preventing neutrophil function
Matrix Metalloproteinases (MMPs)	Tetracyclines[115]	Chelate Zn2+ ion of zinc-dependent MMPs
Interleukin-8 (IL-8)	Repertaxin[71 72]	Currently used as a chemotherapeutic agent for multiple malignancies
	Sivelestat[73]	Suppresses IL-8 production in granulocytes and inhibits neutrophil elastase; indicated in the treatment of acute respiratory failure
Interleukin-17 (IL-17)	Secukinumab (NCT03713632), Ixekizumab[63,64]	Anti-IL-17 antibodies currently indicated for the treatment of psoriasis, psoriatic arthritis, and ankylosing spondylitis; phase III trials are currently underway testing secukinumab's safety and efficacy in the treatment of HS
	Bimekizumab (NCT03248531)	A dual IL-17A and IL-17F inhibitor; currently in phase II trials for moderate-to-severe HS
	Brodalumab[65] (NCT03910803)	Unique blockade of IL-17A, IL-17C and IL-17F; showed promising results for HS in open-label cohort study
Interleukin-1 (IL-1)	Anakinra[81,82]	IL-1 receptor antagonist; some experiences of severe HS proving refractory to anakinra
	Bermekimab[83] (NCT04019041)	Anti-IL-1α antibody currently undergoing phase II trials for the treatment of HS
	Canakinumab[84-88]	Anti-IL-1β antibody; has demonstrated mixed results for HS
Interleukin-36 (IL-36)	BI 655130 [77]	No IL-36 inhibitors are currently under testing for HS; phase 1 proof-of-concept study involving patients with

		generalized pustular psoriasis treated with BI 655130, a monoclonal antibody against the IL-36 receptor (NCT02978690), showed good results
Lipocalin-2 (LCN-2)		Currently, no medications directly targeting LCN-2 exist on the market or in clinical trials.
Leukotriene B4 (LTB4)	Ubenimex[96,97]	Also has subtle inhibition effect on MMPs
	Zileuton[125]	Inhibits 5-Lipoxygenase (5-LOX) enzyme in leukotriene synthesis pathway; currently undergoing phase II trials for the treatment of moderate to severe inflammatory facial acne
	Atreleuton, Setileuton[98]	Similar to zileuton in mechanism of action and indication; currently in clinical trial stages for multiple respiratory diseases
Platelet-Activating Factor	Rupatadine	Synthetic PAF antagonist that is currently indicated for the treatment of severe allergies & chronic idiopathic urticaria
	Natural PAF antagonists[102,104]	Includes ginkgolides, alpha-bulnesene, and andrographolide; Mediterranean diets, as well as those incorporating garlic, soy sauce, turmeric, and tea
Kallikrein	Ecallantide[110]	Selectively inhibits the activity of plasma kallikrein; indicated for the treatment of hereditary angioedema

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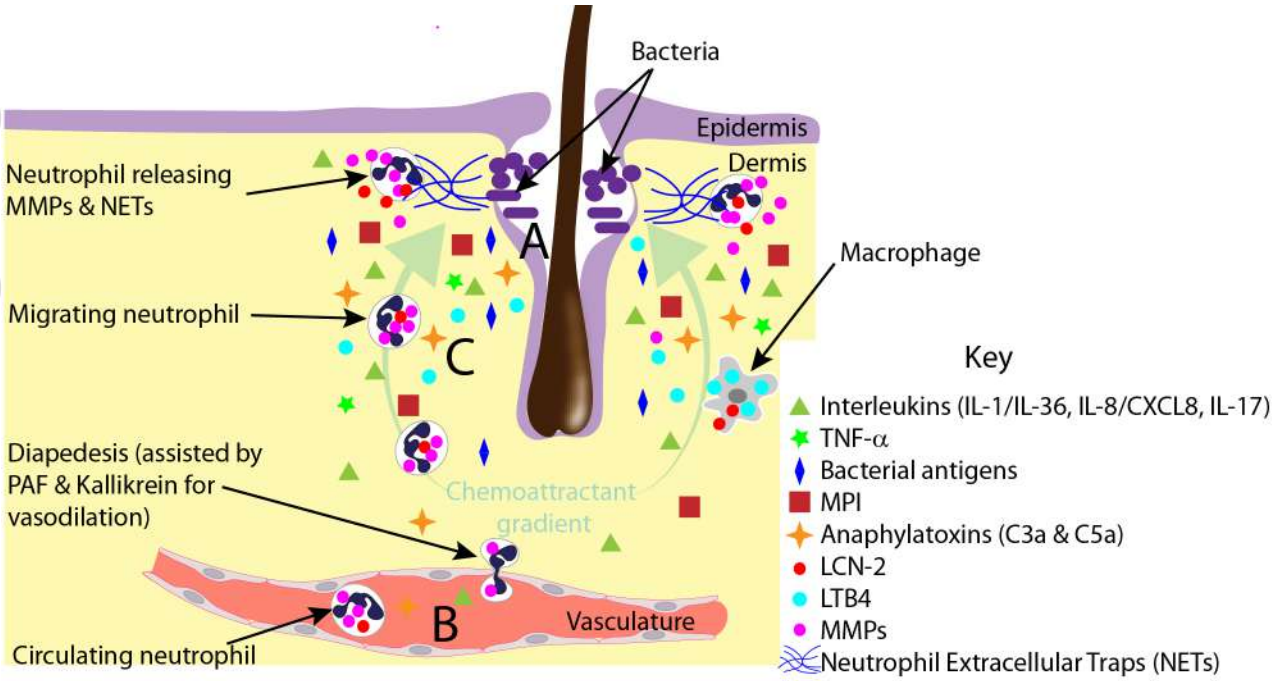

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